

The Development of Pharmacodynamics as a Pharmaceutical Science: A Personal Perspective

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It was a day in the early 1950s at the University of California School of Pharmacy in San Francisco (UCSF) when I saw my fellow undergraduate student Bert Ballard staring intently at a large, water-filled glass beaker containing goldfish. Responding to my expressed curiosity, he explained that the lateral nerve in goldfish controls the animal's balance and that it is very similar to the eighth cranial (hearing) nerve in humans which does the same. Bert was studying the effect of the potentially ototoxic antibiotic streptomycin on balance in the fish under the guidance of Dr. Dufrenoy, a visiting French pharmacognosist. I thought that the apparently off-balance goldfish were simply leaning into the curve (like a race car driver) as they circled in the beaker but kept my mouth shut. I forgot all about this encounter until several years later, but discuss more about this in a subsequent paragraph.

When Harvey Whitney Jr. asked me to contribute an article to the 40th Anniversary Edition of *The Annals*, I reacted with mixed feelings. On one hand, I consider Harvey a friend, and I admire his and his staff's accomplishments in making and keeping *The Annals* a cutting-edge publication and, in my opinion, the most valuable journal for clinical pharmacists and of great value also for other pharmaceutical scientists and clinical pharmacologists. These were strong enough reasons to accept Harvey's invitation. On the other hand, I am now 78 years old and I have given away almost all of my professional library and discarded my files and records. I live in a small town (Sarasota, Florida) without a Health Sciences Library nearby, and the Internet is not of much help for recalling the old days. What finally convinced me to undertake this writing assignment was an email from Associate Editor Eugene Sorkin, who told me that "it would be good if you could somehow impress upon our new practitioners and graduates that what they take for granted today has not always been that way."

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I am probably the sole survivor of the first generation of American academic pharmacokineticists and pharmacodynamicists and therefore feel an obligation to my colleagues past and present to recall some of the early events that are part of the development of pharmacodynamics (PD) as an important component of the pharmaceutical sciences. There are a number of reviews that track the global development of the older science of pharmacokinetics (PK) and I will not deal with that subject. PD, as I see it, is concerned with the quantitative, temporal aspects of drug action, and particularly with the relationship between the concentration of drugs (and their active metabolites) in plasma or other biologic fluids and the intensity and time course of their pharmacologic effects. This will not be a definitive historical review, but rather a personal recollection of the academic environment and of certain seminal events in the early days of PD. I hope that readers will forgive me for any errors of omission or commission.

Pharmacy in the early 1950s was largely chemistry oriented. Scientific vigor in pharmaceuticals developed only slowly. Pharmacology was taught mostly as a basic scientific discipline with little or no consideration of clinical aspects. Students working in pharmacies were instructed by their preceptors not to discuss the identity and indications of prescribed medications with clients. Many students who sought a more clinically oriented experience transferred to medical school.

At UCSF, 2 young assistant professors, Eino Nelson and Sidney Riegelman, recognized the urgent need for a more realistic curriculum and developed a lecture-and-laboratory course based on physical chemistry, pharmaceutical formulation, and pharmacokinetics as the core of an optional doctor of pharmacy degree program for a selected small group of students. I was invited to join that program and also to become an investigator, under the direction of then assistant professor Werner Schwarz, on a US Army-sponsored research contract to develop surgical lubricants that are stable at low temperatures (the Army was preparing for

the eventuality of a hot war in a cold climate). My research at UCSF, during and after my PharmD studies, focused largely on hydrophilic polymers and involved only limited clinical evaluation. We did, however, develop a very useful bioadhesive formulation, even though the term bioadhesive was coined only about 20 years later!

As Eino and Sid introduced us to the fundamentals of PK and rational pharmaceutical formulation, I would often ask myself about the quantitative implications of the effect of variations in pharmacokinetics and bioavailability on therapeutic efficacy. Try as I may, I could not find any definitive information concerning the relationship between drug concentration in plasma (or other biologic fluid) and intensity and time course of drug action in journals and books. I still remember my disappointment when, even some years later, there was no mention of this subject in the classic textbook *Principles of Drug Action* by the Stanford group of Goldstein, Aronow, and Kalman or in Goodman and Gilman. There were, of course, many studies of isolated organs and tissues in baths of known and constant drug concentration (no drug concentration measurement was needed!), but these were not helpful. I spent most of my spare time at UCSF in the library scanning the clinical literature for graded and repetitive measurements of drug action in the hope that some day I may be able to model such data.

My richest source of data at that time was in the area of analgesics, the comparative efficacy of which was a subject of intense commercial interest and study sponsorship. I could not have picked a more complicated subject (which I pursued until my retirement with rather limited success). However, I noticed something rather surprising: the rate of decline of the analgesic effect after drug administration was essentially the same as the rate of decline of the placebo effect *in any one study*. This was true for narcotic as well as non-narcotic analgesics. I first reported this observation in 1961 and eventually at the Fifth International Congress of Pharmacology in 1973 and concluded that the time course of clinical analgesia is characteristic of the effect itself rather than being related to the time course of drug concentrations. I was not smart enough to develop this conclusion to the point of suggesting the existence of an endogenous analgesic substance, but upon subsequent discovery of the endorphins and enkephalins I proposed (with some support from studies by others and ourselves) that analgesics as well as placebos (the latter in man only) displace endogenous opioids from inactive binding sites and make them available for interaction with opioid receptors. However, I know now that matters are much more complicated than this (particularly with respect to placebo effects), and there are alternative explanations that are beyond the scope of this article.

By 1958 I had assumed a faculty position at the School of Pharmacy at the University of Buffalo (now the University

at Buffalo, State University of New York) which, like many American pharmacy schools in the 1950s and 1960s, did not have a graduate program, was very poorly equipped, and had a faculty not oriented toward research (a situation that started to change drastically in the 1960s after Daniel Murray became dean). I was able to interest a number of bright and very motivated undergraduates (including future professors Richard Reuning and William Jusko) in research despite our very modest equipment (I had been given a budget of about \$1500, which bought a colorimeter, analytical balance, viscometer, and constant temperature water bath). That was enough to start a series of studies on dissolution rate-limited drug absorption and led to the now widely used beaker dissolution test method (USP Apparatus 2). Studies on animals were a bit more difficult considering our limited resources until I recalled the goldfish experiments at UCSF. In thinking about what my undergraduates would have time to do and what out-of-pocket expenses I could afford, I thought about the fish-in-a-beaker as a PK/PD system that could be characterized by onset-of-effect data alone.

When the first dissolution study (on the physical-chemical basis of the at that time intense buffered aspirin controversy) was accepted for publication in the *New England Journal of Medicine* and the first goldfish study made it into the *Journal of Pharmacology and Experimental Therapeutics*, our credibility and resources started to increase appreciably. Other pharmaceutical scientists, such as Milo Gibaldi and John Wagner, became interested in studies on goldfish and made significant contributions. Years later, my former graduate student William Hayton (who later became chairman of pharmaceuticals at Ohio State), recognizing the importance of environmental toxins in fish used for food, raised these studies to a considerably higher level of sophistication.

During all of this time, I continued to reflect on the relationship between PK and the time course of drug action. Despite my earlier exposure to the complexities of the kinetics of analgesic effects, I still believed that it should be possible to model PK/PD relationships of many drugs. To my delight, I found a rich source of PD data in the anesthesiology literature. Anesthesiologists were monitoring the time course of neuromuscular blockade following parenteral injection of drugs such as tubocurarine and succinylcholine and were exploring empirically different dosing regimens to optimize patient recovery time after surgery. Unfortunately, they did not or could not measure concurrent plasma concentrations of these drugs. As before, I had to deal with effect intensity data without the corresponding drug concentrations, but these efforts eventually yielded several valuable PD equations.

It was customary in those days to represent dose (or tissue bath concentration) versus pharmacologic effect intensity data in semilogarithmic form, that is, as log dose or

concentration versus effect (the latter on a linear scale in absolute terms or as a percentage or fraction of the theoretical maximum effect). Such plots were essentially linear within the 20–80% effect range so that the relationship could be characterized by a slope and intercept equation. Combining this equation with the PK equation for simple first-order drug elimination yielded an expression that predicted that, with the stated assumptions, the pharmacologic effect intensity should decline at a constant rate, that is, by zero-order kinetics, with the rate being a function of the log concentration–effect slope and the drug elimination rate constant. I published this equation in 1964, and I have been told by colleagues that they consider it the first formal equation in PD. This was followed by equations for the second dose effect and for the relationship between dose and duration of drug action, the latter yielding estimates of the minimum effective dose for a given effect intensity and of the first-order rate constant for drug elimination, both estimates being made without chemical assay! By 1967, when the first issue of *The Annals* (then called *Drug Intelligence*) appeared, I had just published my first comprehensive review of these PD equations and demonstrated their fit to clinical and animal data. In this review, which appeared in *Clinical Pharmacology and Therapeutics* in 1966, I also considered multiple doses and special cases of drug absorption. As a follow-up, Milo Gibaldi, I, and then graduate student Howard Weintraub published a review in the same journal in 1971 in which we addressed multicompartment PK/PD systems in which the site of drug action was located in either the central or in a peripheral compartment.

Much has happened in PD since then. Physicians whose interests focused on measuring pharmacologic effects, chemists and pharmaceutical scientists who could develop specific and sensitive methods for the determination of drug and drug metabolite concentrations in biologic fluids, and pharmacokineticists interested in PD began to speak to one another and to collaborate with each other, particularly in industry. At Buffalo, California, Michigan, Uppsala, and a few other pharmaceutical research centers, graduate students were being trained not only in PK theory, but also in its experimental aspects. Consequently, we became less dependent on literature data to stimulate or confirm studies on PD theory. In 1968, the distinguished pharmacokineticist John Wagner published an important paper in which he showed that many drug concentration–effect relationships could be fitted to the Hill equation over the entire effect intensity range. This was an obvious and timely (as computers were becoming more widely available) improvement over the log-linear correlation provided that very accurate data were available at the extremes of the curve. Many years later, William Ebling (then at Buffalo) showed that, without such data (which are often difficult to

obtain for technical reasons), parameter estimates could be substantially incorrect. This problem remains a challenge for investigators to this day.

I was fortunate to meet, early in my career, Robert O'Reilly, a physician–hematologist associated with Stanford University who was doing extraordinarily interesting and important research on the PK and PD of the coumarin anticoagulants in humans. Equally fortunate, I met a clinical pharmacologist, Aryeh Hurwitz, at his laboratory in Kansas City, where he showed me how to draw repeated small blood samples from rats. Coumarin anticoagulants appeared to be ideal for PK/PD studies in small animals: both the anticoagulant effect and the plasma concentration of drugs such as warfarin and dicumarol could be determined in small blood samples. We were able to take 12 or more such samples from a single rat and restudy the same animal in crossover experiments a couple of weeks later. Initiating these studies, which eventually resulted in over 50 publications in 35 years, was a particularly talented graduate student from Japan, Renpei Nagashima, who is now the president of an important molecular biology research institute in Tokyo. Our initial aim was to compare the PK/PD of warfarin in man and rats. The anticoagulant action apparently lagged the plasma concentrations by one or two days. Using the excellent clinical data obtained by Dr. O'Reilly, we developed a PK/PD model that characterized the prothrombin complex activity (PCA) at any time as the net result of 2 opposing processes, namely the synthesis and normal degradation of vitamin K–dependent clotting factors. Warfarin (or any other coumarin anticoagulant) inhibits the synthesis process in a concentration-dependent manner in both humans and rats. This model was the first of a very important type, namely, indirect effect models. Eventually, in the 1990s, my former graduate student and by then faculty colleague William Jusko and his students extended this model in a brilliant series of studies that have encompassed a wide array of PK/PD systems. I consider this work as the most important conceptual contribution in the history of PK/PD to date.

One of my problems in the classroom was to explain to the students the usually small (minutes to hours) lag between plasma concentration and pharmacologic effect profiles (hysteresis). In 1979, the late Lewis Sheiner, a clinical pharmacologist at UCSF destined to become an intellectual world leader in PK/PD, and Donald Stanski, an anesthesiologist with an educational background in pharmacy who later developed an outstanding record of PK/PD research at Stanford University, formulated a PK/PD model that rationalized PD hysteresis by defining a multicompartment system that included a hypothetical effect (site of action) compartment. This model became very popular and, together with the Hill equation, was for many years the standard for PK/PD modeling. With the introduction of indi-

rect effect models and greater insight into the mechanistic aspects of PD, the emphasis is now shifting to indirect effect modeling when appropriate.

While still at UCSF, I used to follow the literature via one of the sections of *Chemical Abstracts* (In those days, one could subscribe to a personal copy that even a student could afford!). I came across an abstract in an obscure journal that described a bell-shaped concentration–effect curve in insects. Upon my request, the South American author sent me a copy of his paper along with a note asking if I had encountered anything like this and if I had any explanation for this type of curve. My answers were no and no, but almost 25 years later, in 1979, Lennart Paalzow of Uppsala University reported on several drugs, including clonidine, that exhibited a biphasic effect. He showed that this can be due to 2 types of receptors eliciting opposite effects (such as increasing and decreasing blood pressure) over different (though possibly overlapping) concentration ranges.

By 1980, the basic tools of PK/PD had been developed and investigators were focusing on more specialized and demanding aspects of the discipline. Population PK, pioneered by Lewis Sheiner and Stuart Beal at UCSF, was extended to include population PD. At Buffalo, Jerome Schentag developed the concept of dual individualization of antibiotic dosage based on an individual's PK and PD characteristics, the principles of which apply equally to other drugs; Ho-Leung Fung and his students performed comprehensive PK/PD studies of the cardiovascular action of organic nitrates with emphasis on exploring the mechanism and modeling the development of acute tolerance; and Bill Jusko and his students focused their research increasingly on a detailed investigation in intact animals of the kinetics of drug action on a receptor level, with particular emphasis on the glucocorticoids. Nicholas Holford, formerly at UCSF and now in New Zealand, modeled the progression of chronic diseases, like Alzheimer's, such that drug action could be characterized as a function of time despite a shifting baseline. Lewis Sheiner, Donald Stanski, Richard Lalonde, and many others developed the technique of clinical trial simulations, an increasingly important tool in drug development.

In the early 1980s, I decided to explore the potential influence of underlying diseases on drug action. I was very fortunate to have a post-doctoral fellow from the Netherlands, Meindert Danhof, join us to start off this effort. Meindert was sent to me by Douwe Breimer, then Professor and Chairman of the Department of Pharmacology at Leiden University and presently the University's Rector Magnificus. Douwe, an international leader of pharmaceutical science, had been instrumental in converting the School of Pharmacy at Leiden into a world-class graduate and postgraduate research center and was preparing for the development of a PD group in the Center. Meindert turned

out to be an outstanding and productive scientist who made very important contributions to our project. Since his time at Buffalo, he has become professor and chairman of pharmacology at Leiden, where he has built an outstanding center of PK/PD research, broad in scope and of international reputation. He and his students have developed many novel methods for measuring drug effects and have emphasized the quantitative relationship between receptor pharmacology and in vivo drug action. My project on the kinetics of drug action in disease states continued for 10 years until my retirement. The Esteve Foundation recently reprinted the 45 publications of this project as a book that was sent gratis to health science libraries throughout the world.

These are some of my recollections of the early days of PD. They are of necessity random and incomplete, and should not be taken as a definitive history of the early days of PD.

What lessons have I learned from my experiences as an academic pharmaceutical scientist engaged in PK/PD teaching and research? Here are some:

There is no excuse for an academic to not engage in research. Lack of resources, a high teaching load, limited laboratory space, and lack of graduate students can slow progress, but should not be alibis for not getting started.

Do not be overly reductionist in your research and try to think in an interdisciplinary way.

Stay close to your students and learn with and from them.

Seek clinical collaborators, but stay away from empire builders.

Keep things simple. Do not get bogged down by complex methodology or instrumentation if you can help it.

Write your scientific reports to inform, not to impress.

Remember that the aim of PK/PD is to improve pharmacotherapy. This focus on patients should be at the heart of designing, performing, interpreting, and reporting PK/PD research.

As I look through the pages of current issues of *The Annals* and reflect on its gradual transformation over the last 40 years, I can recognize a focus on patients as the driving force of that transformation and the reason why readers find the journal so valuable. In wishing its publisher, editors, and staff continued success, I recognize that this focus will continue to contribute greatly to better and safer pharmacotherapy for the ultimate benefit of patients.

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Reprints available from *The Annals*.

Published Online, 14 Feb 2006, www.theannals.com
DOI 10.1345/aph.1G510